Gay, William 1992

Dr. William Gay Oral History 1992

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Dr. William Gay, formerly with the Animal Resource Program of the Division of Research Resources at the NIH, discusses the use of animal models in medical research and the improtance of Simian AIDS in understanding HIV. He describes the work of the U.S. regional primate centers and the outbreak of SAIDS in 1981. He discusses the development of research on SIV (Simian Immunodeficiency virus) and other animal immunodeficiency viruses. He also indicates his own background as a veterinarian.

This is an interview with Dr. William I. Gay, who formerly worked at the NIH. His last position was at the Animal Resource Program (ARP) of the Division of Research Resources, National Institutes of Health (NIH), Bethesda, Maryland. The interview was conducted in the NIH Historical Office on 15 July 1992. The interviewer is Dr. Victoria A. Harden, Director of the NIH Historical Office.

Harden: Would you begin by talking about your own background--your education, and why you became a veterinarian?

Gay: I grew up on a farm in upstate New York, at the north edge of the Catskills, where I worked with livestock. If you were a farm boy and did not have any money, you could go to a state school like the veterinary college because you did not have to pay tuition. I worked my way through Cornell [University] from 1944 to 1950 and earned a DVM [Doctorate in Veterinary Medicine]. When I got through, there were lots of jobs for veterinarians--more than there are now. I indicated to one of my professors that I needed experience in treating small animals, so I went to work for a small animal practitioner in New York City. Now, I mean Queens, not Manhattan. The practice was located halfway between JFK [John F. Kennedy Airport] and La Guardia Airport. JFK was known as Idlewild Airport in those days. They were building a big connecting road right through our practice (animal hospital) area. We had a lot of business. I worked with cats, and with the more unusual animals that came into the practice. The old timers did not really care for cats and birds; they were happy to give those cases to a young, flexible guy.

When I was in college, World War II was on, and I came up for the draft. Because I had a low renal threshold for sugar, the authorities kept saying, "You've got diabetes; we won't take you." I was deferred and went to school. In 1950, when I became eligible for the doctors' draft for Korea, they said, "You were deferred and went to school." I said, "No. I was deferred because of a physical problem." "Ah, but you were deferred and went to school." Well, my number came up and, so in order to get around all of this, and to avoid going in as a foot soldier, I joined the Veterinary Corps as a first lieutenant. Those in charge looked over my curriculum vitae and said, "This guy has been in small animals. We'll send him to that laboratory animal place at Walter Reed [Army Medical Center]." It was the best thing that ever happened to me.

At Walter Reed, there were rats and mice with all kinds of health problems. The Center had lots of dogs. We were in the middle of the Korean War at this point and were working on technologies which would be used by the MASH [Mobile Army Services Hospital] hospitals. The movie MASH, is the real thing. As a matter of fact, I shared an office with "Trapper John" in the NIH Westwood building for a while, and I saw those pictures before they ever made the movie. Those hospitals were the real thing, and we were working on technologies like kidney dialysis. At that time, one theory held that shock produced some product in the blood that could be dialyzed out with an artificial kidney. We had artificial kidneys operating as close as two miles from the front; but they did not protect against shock. Even so, we were able to provide the army medical staff with background studies in animals before they went to Korea. We also worked on problems like replacing segments of long bone, because the firearms that the soldiers were using could do a lot of tissue damage. If the bullets went through a bone they blew it apart, and a segment would have to be replaced. I got some nice papers out of that work.

While I was at Walter Reed, I made friends with Dr. William (T.S.) Thorpe, who was in charge of what is now Veterinary Resources. They were building the NIH Clinical Center and the animal facilities south of the Clinical Center. Bill was looking for somebody in experimental surgery. I came to the NIH in 1954 for that job and I stayed in what is now Veterinary Resources for nine years. The place grew so much during those nine years that I found myself doing administration full time. I accepted an opportunity to move to the extramural program in administration with Dr. Willard Halsey (Hal) Eyestone, who was a well-known veterinary pathologist in the Division of Research Resources. I was with various extramural programs from then on--NIGMS [National Institute of General Medical Sciences] for four years, Allergy and Infectious Diseases [National Institute of Allergy and Infectious Diseases, NIAID] for ten years, and DRR [Division of Research Resources] for eight years.

Harden: You were in DRR in 1981 when AIDS was identified as a new disease. Before we discuss AIDS, however, could you define what an animal model is? How do people go about selecting one? What are the problems, etc.?

Gay: There are lots of people, especially animal rights people, who do not want you to do animal research. They love to quote, "The best study of man is man and mankind." That is true. But if you examine the Helsinki Accord, which came about after the World War II atrocities, you learn that one does not do experiments on people. Of course, we have followed that way of operating at the NIH since the turn of the century. There are many things that we use animals for before you go to the clinic. The basic point to remember about animal research is that animals are part of a spectrum of biological species. Somebody has an idea about, say, liver function, and you can get a little information, perhaps, from an isolated liver. You can get an idea from the isolated liver and the liver cell; but do not forget that the liver is functioning under the direction of the pituitary gland, the adrenals, and many other enzymes and hormones. Because of this, before you move into the clinic to apply your findings to humans, you want to test them in some similar creatures. What you do is to look through everything you can find in the literature about liver physiology. You may see that the woodchuck has a hepatitis virus. The cat gets cirrhosis. You then look around to see which animal has liver function most similar to that of the human. Even if sometimes the animal's function is not exactly similar, out of desperation you use the animal, because if you can define a biological principle in the mouse, and then if you find that the same principle applies in the rat, the dog, and the primate, it is pretty safe to move to the human. If the principle does not hold for each case, physicians must be very cautious before moving to the human. That is the animal model business. Comparative medicine in a nutshell is confirming your findings in a variety (spectrum) of species.

A good illustration of this is the thalidomide story. You are in the history business, so you remember thalidomide? This drug, when taken by pregnant women, caused babies to be born with no limbs. In humans, thalidomide restricts the formation of the limb buds during the evolution of the embryo, resulting in very short limbs. Thalidomide was developed in Germany, thoroughly tested on rats and mice, and then was moved right into the clinic. It was a marvelous tranquilizer, especially for women who had hormone-related stress and behavioral problems. Many people in Europe were using it. It was licensed there right away. People wanted to have it here [in the United States]; they wanted it very much.

When the application for an IND (Investigational New Drug) came in to the Food and Drug Administration [FDA], it went to the desk of a Dr. Frances Kelsey. Dr. Kelsey had been at the FDA for a long time. If something got on her desk, some said that it never got off. It was delayed and delayed, and it was all Dr. Kelsey's fault. But Dr. Kelsey was a stickler for details. She looked at the thalidomide protocol and said, "It hasn't been tested on any higher animals." Studies were thus run on dogs, with no adverse effects. Dr. Kelsey, however, said, "I want to see what it does in primates." When the studies were conducted, the baby primates were born with severely shortened limbs. If the Germans had ever tested thalidomide on monkeys, it never would have been marketed. Since the drug was legal in Germany, it was brought to the United States, carried in by a number of people, and so it inflicted some damage on embryos in the U.S..

This illustrates that if you believe you understand a biological principle but it does not apply to a spectrum of species, watch out before you go to the clinic. This was a real "watch out." That is why something like RU486 needs to be tested thoroughly on primates. The Primate Center in Oregon and one other center, have worked on RU486, and it appears to be pretty safe. In the end, testing a few monkeys is as important as many of the other tests in the laboratory.

Harden: It sounds as though you have a much better theoretical basis today for choosing an animal model than investigators had early in the twentieth century.

Gay: That is right. There is another thing that you can also do, which especially relates to AIDS. Did you see in Science in the last few weeks about the pigtail macaque as a model for AIDS? That is a marvelous illustration. Researchers looked at the literature about this monkey and also took the monkey cells to the lab. They used the cells from different species to see if the virus would infect the white cells in tissue culture. It would in the pigtail macaque, and that is why they went immediately to the pigtail macaque as a model for AIDS.

Harden: Have the animal rights groups had any impact on the kinds and numbers of animal models that are available?

Gay: They have not had any effect on the kinds and numbers of models available. But they have had an impact on animal use and it has become infinitely more expensive to use animals because of all the regulations. Many institutions now spend $100,000 a year on security. The NIH spends more than that because they are afraid of break-ins and so forth. Many people predict that the numbers of animals used in medical research are going to decline. I had a professor in pathology who used to say, "You know, Bill, there are three kinds of lies: lies, damn lies, and medical statistics." You have to watch those medical statistics even when applied to laboratory animals.

What is happening is that a smaller number of animals is being bred for research, and probably smaller numbers are coming into the supply. What is getting bigger is the inventory. In many diseases being studied now--AIDS is a good example--it may take the animals anywhere from ninety days to a year to come down with the disease or show a pathological change. In the old days when we were working with influenzas, for example, the animal would be in and out in about four weeks. Now we are keeping them around for eight months to a year. This means that there is a tremendous inventory problem in the animal research business. When an administrator reads that there are smaller numbers of animals going into medical research, he or she says, "Why, then, are the costs going up?" The inventories are increasing. That is why.

It is also more expensive to use transgenic animals that can now be specially prepared and bred. When you prepare about a hundred ova and inoculate them into mice or cows or whatever you are working with, and your yield is, at the most, five infants and one or two adults, this costs a lot of money. But once you reproduce those animals, you keep them around a long time. This means that many types of animals are accumulating. Although there are not many more animals going into research, the inventory does increase. Probably there are not more than 10 percent more animals used, and produced for research, this year than in 1985. If you look at the inventory, however, it is probably up 25 or 30 percent.

Harden: In your article on the history of the regional primate centers, you noted that the inspiration for these centers came when Dr. James Watt visited the Soviet primate centers in the 1950s. What was it about that trip that impressed him to create such centers and why did we end up with seven instead of one?

Gay: [Dr. James] Shannon was very sensitive to the regional philosophy. There is a history of the primate centers that [Dr. Leo] Whitehair and Animal Resources and Comparative Medicine wrote together, and they are producing another one now. [Dr.] Paul Dudley White was [President Dwight] Eisenhower's heart specialist, and he wanted to know what the Russians were doing in this area. He and Dr. George Burch from Tulane [University] were invited to the primate center in Sukhumi on the Black Sea, which is now in Georgia. Incidentally, since the breakup of the Soviet Union, the Georgians have thrown the primate center out. Dr. Boris Lapin was the director of the center until the breakup of the Soviet Union. Some of the baboons have been moved to a nearby Russian city called Adler.

During the 1950s Dr. Boris Lapin was producing various cardiac difficulties in the baboons. Because of their interest in heart disease, the Americans became acquainted with Boris, who spoke very good English. The Americans were very impressed with what had been done at the Soviet center over the years. They came back and said, "We should have a primate center like that to study heart disease." This is why primate research was launched in the Heart Institute [National Heart, Lung and Blood Institute, NHLBI]. Although primate research is not any more related to heart research than it is to infectious diseases or metabolism or mental health, it started in the Heart Institute because of this trip by Dr. Paul Dudley White and Dr. Burch. It was Dr. Shannon's interest in the regional distribution of research that led to the creation of seven centers. At that time, the NIH budget was expanding at a tremendous rate.

Harden: In Dr. Murray Gardner's informal summary of the 1986 symposium on Simian AIDS, he noted competition between the centers. He implied it was not insignificant. Would you describe this competition?

Gay: It is the same as the competition between Bob [Dr. Robert] Gallo and [Dr. Luc] Montagnier. Everybody wants to be first.

Harden: Did the centers work on the same problems or did different centers address different problems?

Gay: You have to remember that this article was discussing Simian AIDS [SAIDS]. The disease appeared in at least three centers more or less at the same time. But it did not appear as the same disease. In California, it looked rather like AIDS, with the lymphatic increase, the gradual loss of weight, and then death due to some microbial infection. At the primate center in Washington, it was a disease of the peritoneum, and it showed up first as red cell or as white cell deposits on the peritoneum. It was first called retroperitoneal fibromatosis. This condition would gradually get worse and worse, and the monkeys would die in somewhat the same way. There was yet another manifestation of it at the Oregon center. The people at the New England center were very intrigued with this in late 1982. They were looking for Simian AIDS in some macaques that they had purchased. I believe that New England also had some cases early on. Eventually the centers found that there were three retroviruses of the macaques, and the one that most closely resembled the present day SIV [Simian Immunodeficiency Virus] was the one in California, which was isolated by an NIH researcher named Dr. John Sever in the Neurology Institute [National Institute of Neurological Diseases and Stroke, NINDS], and [Dr.] David Madden, a veterinarian who worked for him.

Harden: Before we discuss the details of Simian AIDS, I want to ask one more preliminary question. Can you give us an overview of the kinds of problems the regional primate centers were working on before AIDS was identified in 1981?

Gay: The centers are unique in that the NIH built the buildings, but each had its own emphasis and organizational structure. The New England center, like everything in New England was dominated by Harvard [University] and was built by them out in the country. It was a free standing operation for both New World and Old World--that is, Asian--primates.

In the case of the center in Atlanta, Emory University proposed to the NIH that they would create the Yerkes Center. It would be based on the primate colony formed by Professor [Robert] Yerkes at Yale in about 1928. The facility was almost as old as the Russian Center. Emory brought the Yale chimpanzees to Atlanta from Orange Park, because Yale was anxious to close the facility which was old and deteriorating. In the late 1950s, a number of Georgians were associated with the NIH, including [Dr.] Ernest Allen and Boisfeuillet Jones. They were delighted to put a center at Emory. It has been a very successful center.

Another center was located at Tulane. Since George Burch from Tulane had been a key person in establishing the primate centers, Tulane had to have one. The Oregon people, who already had a small center outside of Portland, came in with an excellent application, as did Wisconsin with [Dr.] Harry Harlow, the behavioral scientist who conducted the famous terry-cloth mother experiment. California also came in with an excellent proposal for Davis [University of California at Davis]. In the beginning, each of the centers tended to have rhesus macaques somewhere. But two of them, Tulane and Atlanta, had chimpanzees. A number of them had New World monkeys and the people in Oregon had some lemurs--these beautiful animals with the raccoon-like tail from Madagascar. The people at Tulane also worked hard at having New World monkeys, so, to some extent, they had different types of animals.

Now, what kind of research did the centers do? Yerkes, having chimpanzees, worked a great deal in the behavioral science area. The studies that I remember best coming out of Yerkes were the language studies. Are you familiar with the efforts to teach the chimpanzees to communicate? The scientists teach the chimpanzees with symbols, such as a symbol for "go for a walk"; a symbol for "food treats"; a symbol for "walk in the woods"; and a symbol for "visit with Sally, the chimp next door." Once the chimpanzees had learned the symbols, the scientists wanted to see if they could communicate with one another. Sure enough, they could. That is a marvelous basic science principle. What could one do with it? Suddenly, somebody thought of a way to use the information. They taught retarded children the symbols, and added a voice synthesizer to the symbol board. Using the various symbols, a retarded child could be more independent--he or she could take the bus to school, for example.

The center at Tulane was interested in infectious diseases. The people there have done a lot of good infectious disease work, mainly virology. The center in New England is the only one that has been associated with the Nobel Prize. [Dr. Torsten] Weisel and his colleague, Dr. David Hubel, were very interested in vision. They studied children who did not use one eye or had other vision problems. Drs. Weisel and Hubel showed that if the developing eye does not get visual input, the part of the brain associated with the interpretation of vision does not develop. That probably applies to many other things, as well. They won a Nobel Prize for this work.

The people at the Wisconsin center also worked largely with behavior. This was where Dr. Harry Harlow studied mothering and the development of behavior. Dr. Ted [Theodore] Ruch at Seattle was interested in physiology. That turned out to be a great thing, because Washington had the best bioengineering operation. When I was at NIGMS, and later at NIAID, the Washington center had the best bioengineering operation available. These men could rig up a primate with a little box so that the animals could walk around and they could still transmit all kinds of physiological data.

Each center developed according to the way their institution wanted them to. At Oregon, there was a fair bit of behavior research; there was a lot of comparative anatomy; and there was some nutrition research. I am sorry but I do not remember anything about other research at the California center. AIDS came to dominate research at California so much in my memory. The center did quite a bit of environmental toxicology.

Harden: One of the things we have noted is that AIDS thrust these centers into the limelight and led to a dramatic increase in their funding. In your notebook on the history of the centers' role in AIDS you implied that, before AIDS, funding had been very tight and that people did not always realize the importance of these centers. Could you elaborate on this?

Gay: When I prepared the history, I had just finished being the bureaucrat who had the primate centers as one of his responsibilities, trying to get them a little more money each year. That probably influenced my text somewhat. Frankly, I do not think the centers were ever grossly underfunded. There were, just as for other parts of the NIH research community, opportunities to which they could not respond because of limited resources. But the centers always remained ready to move on to something new, and they had just enough backlog of resources to be able to do so. That was the nice thing for an investigator who could go to one of the centers with a few bucks, because they could assist with a new initiative very quickly. So, I would have to say in all fairness that I am not sure they were ever grossly underfunded.

AIDS made a big difference, however, because the centers were in the front line of a very major health problem. Many of the people there realized what a health problem they were up against. There is a man who ought to be more famous around NIH than he is named Bob [Dr. Robert] Huebner. If you talk with Dr. Murray Gardner you can understand why. Murray is always so enthused. Have you ever watched the Boston Pops with Arthur Fiedler? I call Dr. Murray Gardner the Arthur Fiedler of American pathology, because he is always so enthused. He seldom talks about the history of AIDS without getting enthused about Bob Huebner. Bob did a lot with retroviruses in mice. Bob Gallo profited tremendously from being closely associated with everything that Bob Huebner ever did in retrovirology.

Harden: Could you elaborate on the nature of the 1981 outbreak of Simian AIDS? It seems strange to me that it suddenly popped up. The centers had been there all these years. Were they just recognizing it for the first time or was it something really new?

Gay: All of the above. The Washington center reported a problem with retroperitoneal fibromatosis--it was not called AIDS. By 1983 it had been haunting those people for three years. A tumorous lymphadenopathy had also been troubling people in Washington, as well as in California. It had been spreading through their outdoor corrals where the monkeys could get close to one another through the fence. They knew that they were going to have to partition the monkeys off from each other. This disease had been bothering the Washington center since 1979 at least, and they probably did some autopsies on similar cases before that. Fortunately, the California center had saved lymphatic material and sera from the animals since 1976, so they have been able to trace the infection to that year.

Harden: Was the virus that caused the tumorous lymphadenopathy the Simian Immunodeficiency Virus (SIV), or was it one of the other viruses uncovered in the early 1980s?

Gay: Yes, it was SIV. There were two other centers, whose primates also had a Simian retrovirus, but they did not realize it. Their viruses did not become known as SIV because they did not look exactly like the human one. They were not as closely related in their genetic material.

Harden: So SIV was defined through cloning and comparing it with HIV [Human Immunodeficiency Virus].

Gay: Yes. It was pretty close to 1984 before they could do that. Some people's reputations were hurt as they tried to identify an etiological agent for this disease. The pathologist at Oregon really took a bath. He could not get to the bottom of the problem. He could not find any antibodies to anything for which he had an antigen, and there were not any inclusion bodies in any of the cells. That poor man really took a drubbing. The man at Washington had a bad time, too. For some reason, California knew that they had an infectious disease. They were a little more statesmen-like in not blaming each other for it. But there were a lot of personnel problems and infighting over what this disease was; whose fault it was; and what it had done. A new and unknown infectious agent is always a trauma to the staff responsible for the health of a colony. It was a research tragedy, because they were losing some animals that had been on experiment for years. The primate centers tended to house their animals together because they knew it was better for the animals' behavior, for their development, and for their physical condition. Of course, I can remember getting a lecture at our first meeting on Simian AIDS from [Dr.] Ruth Kirschstein: "I never had any trouble like that with my monkeys; I kept them all in single cages."

Harden: Were all of these outbreaks traced to African monkeys that had been imported? The argument was that HIV and SIV must have originated in Africa. Then some importations of Chinese and Indonesian macaques were also infected. How did they get infected?

Gay: I do not know.

Harden: Is it still the consensus that SIV originated in Africa?

Gay: It is still the consensus that it originated in Africa. Many animals have also been imported from China--I think White Sands has brought in quite a few. They have been tested and SIV positives found in them. Who knows where they came from? The Chinese may have accumulated a variety of monkeys for breeding. They might have brought them out of Africa, taken them to China, and ended up breeding them there. It is hard to say, the Chinese are great traders. Max [Dr. Myron] Essex at the Harvard School of Public Health and [Dr.] Preston Marx at the Primate Research Laboratory in New Mexico State at Holloman are the two researchers who have done the most work in determining where the virus came from. They are of the opinion that it came from Africa. I find their evidence and views convincing.

An interesting curiosity in all of this is that the chimpanzee is not susceptible to SIV. It can be infected with HIV, and it will reproduce in them. If you infect an Asian ape, like the Gibbon, with SIV, they get pretty sick, although none of them have died from it. It is not unusual that an African virus which has very limited effect on the African green monkey is very destructive for the Asian macaque. I do not have any trouble with that idea at all.

Harden: This raises the question: Will humans adapt to HIV as they did to a number of other infectious diseases like syphilis, which was very virulent in Europe in the sixteenth century? Adaptation of the host would not eliminate morbidity, but it would reduce mortality.

Gay: Syphilis, gonorrhea, tuberculosis, and other such diseases had survivors who could transmit their resistance. For that to happen with AIDS, there would have to be quite a lot of survivors who could transmit their resistance.

Harden: Do you think Simian AIDS would have remained a curiosity in primates if the human version of the disease had not appeared about at the same time?

Gay: No. I think it would have been such an interesting curiosity at California and such a threat to the colony that people like John Sever would have isolated the virus by 1984 or 1985. Retroviruses are not new, especially for the veterinary world. Swamp fever of horses--equine infectious anemia--is a retrovirus, for example. Dr. Leroy Coggins, now at the University of North Carolina, isolated the viral agent for this disease during the late 1950s. He developed the Coggins test. That virus was spread by veterinarians and trainers with needles. Because of the work of Huebner, of Coggins, and because the center in California was beginning to feel a major economic impact from the loss of animals, as was the one in Oregon, I am sure that it would have occurred to somebody before very long to look for a retrovirus.

Harden: DRR hosted a conference in March 1983 on AIDS in nonhuman primates. This conference addressed both the animal diseases and the disease as a possible animal model for AIDS. Who decided to hold the conference and who organized it?

Gay: Leo Whitehair and I. Leo was in charge of the primate centers. I was on a site visit with him in November 1983. Bob Gallo had not announced his test for AIDS yet. We were in the New England center when it came up. A number of people at the New England center were interested in comparing the pathology of what they were seeing at that time in New England with what the California group was seeing. They also wanted to compare the animal disease with the AIDS infection in humans. The epidemiology of the animal and human disease was so similar that it seemed to us that we had a likely animal model. We took our proposal for a conference to [Dr.] Betty Pickett, who sometimes was pretty strict and could be a stickler for detail like Dr. Kelsey. For some reason she had confidence in Leo and me, and she agreed to our proposal. So we organized the conference. Like everything else related to AIDS, as soon as you mentioned AIDS in connection with a conference, there was immediately a great interest. In fact, there was more interest than we wanted. We had decided to hold the conference in Masur auditorium in the Clinical Center because the Building 31 conference rooms would only hold fifty or a hundred people. We were inviting people from the rest of the primate centers as well as other people. I think it was [Dr.] John Fahey's department in Los Angeles that first informed the CDC [Centers for Disease Control] about the conference. We invited people from both those places. We also had a former clinical director of NIAID, [Dr.] Sheldon Wolff from Tufts University, who was a big booster of the conference. His support was another thing that helped us get approval for it. He thought we were on to something.

The conference was held in early March. Unfortunately, the Masur auditorium holds a lot of people. Before we knew it, we also had fifty press people who wanted to attend. That created a problem. We also had many other people who came in. For example, there was a guy from Ohio with his homosexual pigs. This turned out to be a kind of a hoax. He wanted to participate, but I would not let him speak. He lied to John Sever, who was the chairman, telling him that I had approved it. I had to let him speak. It was a free-for-all. One woman wrote an article on the conference for The New Scientist, a British publication, in which she really roasted us for using it as a forum to "Budget Bust." Let's face it. It was an attempt to improve the funding for this disease in the primate centers. We also thought of the conference as a public service, because we were announcing to the scientific community that an animal model for AIDS had been identified.

Once a virus had been announced as the cause of AIDS, research really took off, and we did make a difference. Leo and I agreed that the next year's conference was not going to be a circus like the one in 1983. We planned to hold our meeting in one of the conference rooms in Building 31 at NIH. We were going to have fifty people and no more. The following spring, a little later in the year than the first one, we had such a meeting. We invited the fifty people we thought we ought to have. But there were many scientists who said they just had to come, so we could not turn them all down. I remember being called on a Sunday morning in my hotel room in St. Louis. It was [Dr.] Raoul Benveniste, making his case for being allowed to come. We finally accepted 110 people to attend that highly restricted meeting. We just could not leave anybody out. From then on the meetings became more formal and less restricted. Now they draw 200 to 300 people a year. Dr. Boris Lapin usually comes from the Russian primate center that was formerly in Sukhumi. I think he came last year. I guess he took up a collection as he went along, but he managed to come. Now there is a fundraiser for his center, because it got all the centers started. It is sponsored by the Washington center. I sent him a hundred dollars, and I suppose I will send him some more. They have raised $3,000 or $4,000 for Boris so far, which will help him a lot. It will probably support a dozen of his scientists for the year. People come from all over the world to the conference. The AIDS animal models meeting is in Puerto Rico this year. It has become an international meeting.

Harden: The tremendous interest in AIDS extends to virtually every field. When we held our 1989 conference on the history of AIDS, we had an experience similar to yours. We scheduled a conference room that would hold fifty people. Many people called me saying, "I just have to come to this conference. A scientist/historian from Italy said, "I must come and tell you what we're doing." We never dreamed that the history of AIDS would have generated as much interest.

You noted that Dr. Sever was the person who named the disease Simian AIDS. When did he do that?

Gay: It was just before the 1983 meeting, but it may not have been much more than twelve hours before. When he wanted to call the etiological agent SIV, I accused him of wanting to call it "Sever's immunodeficiency virus." It was just before the meeting.

Harden: Did he choose the name "Simian AIDS" because it would be good publicity or because it was more descriptive?

Gay: Very descriptive.

Harden: You have noted that animals at the California center provided evidence that the agent was transmissible. What was the evidence, and how early did the researchers see SAIDS as an infectious disease?

Gay: It was by 1982. It was well before the virus was isolated. I cannot tell you whether it was December 1980 or December 1981, but it was well before. The animals were kept in large outdoor corrals, which were about 50 by 100 feet, fenced with cyclone fencing. As the scientists divided the animals, they took strips of land and built the corrals side by side; a middle fence divided them. That was all you needed because the point of the fence was to keep the animals from fighting. The scientists at the California center knew that SAIDS was transmissible because the disease would spread in one partitioned area, then it would show up in the next one and, then it would spread further. That was about as much evidence as they needed.

Harden: Was there any evidence that it was sexually transmitted?

Gay: No.

Harden: Was there any evidence that it was transmitted through biting and scratching? Was blood-blood contact necessary to transmit it?

Gay: I do not know whether they knew that blood-blood contact would spread it, and I do not know how soon they started trying to transmit it by hypodermic needle.

Harden: Essentially, then, by early 1983 they knew that SAIDS was transmissible, but they were not sure of all its parameters and the epidemiology?

Gay: That is correct.

Harden: I raise this because it seems to me that much of the 1983 meeting--the second session especially--was concerned with epidemiology and biosafety. Were there concerns about humans being infected with this agent? Or were the concerns primarily about the spread of the disease among the animals?

Gay: The concern was primarily the spread among the animals. In dealing with infectious diseases of primates, you always worry, because they are so closely related to humans, whether you are going to be the first human to contract the disease. Because of this, you tend to do autopsies in a cap and a mask and a gown and double gloves.

Harden: Primates bite and scratch too, don't they? You must have to deal with that as well?

Gay: You bet. Yes.

Harden: That meant that there were many opportunities for humans to get infected, if the disease was infectious for humans.

Gay: I do not think there was any more concern about that then. There was general concern about monkeys and the agents that they carry. They have a very nasty herpes virus which, in the last three years, has killed two veterinarians. They have an oral herpes virus called Sabin's B virus. They have tuberculosis often. The chimpanzees have hepatitis. I spent the latter part of my first year at the NIH in the Clinical Center with a chimpanzee hepatitis. We all face these things. I do not remember any special concern about that with the Simian AIDS. Everybody continued to be as careful as they always were.

Harden: Looking at some of the comments in the JAMA [Journal of the American Medical Associations] coverage of the 1983 meeting, it is apparent that things were not yet clear. Dr. Gallo had not yet announced his discovery of the virus, and even Montagnier's article came out the month after the meeting. People were leaning at that point towards a virus as an agent, but nothing was settled. Dr. Wolff noted that no sexual differences in the primate victims of SAIDS were observed, yet people were still looking at AIDS as a male homosexual disease. Were the people who worked with primates saying, "This is a virus that could affect everybody," from the evidence that in primates there were no sexual differences in terms of who got it? Was anybody willing to generalize to humans from those data?

Gay: I do not remember whether they did or not. I do not remember anybody pointing out that if animal caretakers were exposed to SAIDS, the human female was likely to be spared.

Harden: Dr. Gene Shearer of NCI [National Cancer Institute], noted that the AIDS-like syndrome in juvenile macaques would be useful in studying AIDS in children, but not in adults. Can you tell me why? Is the immunology that much different?

Gay: No. But, in the macaques with SIV there is a neurological syndrome, especially in the younger macaques, which is very similar to the one in people. I do not think they knew that much about it at that time.

Harden: Much later, in 1986, it was known that SIV infected the brain, and you described it then as an exciting feature. Why were people excited about that fact?

Gay: Because HIV did not make chimpanzees sick, and there was not any model for the neurological involvement in AIDS other than SIV in the macaques.

Harden: There was a great transition period in the history of AIDS after the second DRR conference in March 1984. Dr. Gallo's papers and announcement in April 1984 that a virus was the cause of AIDS were accepted at that time as solving the etiological problem. In November 1984, another meeting on animal models for AIDS was held at the Rocky Mountain Laboratories. Did Gallo's announcement change anybody's point of view on what was going to be discussed about the kinds of animal models you were looking for?

Gay: Yes. To some extent. This November conference was organized by [Dr.] Lois Salzman, who was in the Allergy Institute at that time. She chose NIAID's Rocky Mountain Laboratories in Hamilton, Montana, because we were not able to contain the size of the meetings here in Bethesda and Hamilton is not very accessible. Only the really devout AIDS enthusiasts showed up in Hamilton, Montana.

Harden: Do you have any particular comments about the November 1984 meeting?

Gay: My main comment on the RML meeting is that participants made a real attempt to look at other retroviruses and other animal models. The retrovirus of the cat is not unreasonable. If we did not have monkeys, we would be probably be doing more with one of those retroviruses, such as feline leukemia, for which a vaccine has been developed. I can remember Dick [Dr. Richard] Krause announcing at a scientific directors' meeting that there was no vaccine against any retrovirus. It was most unusual for Dick not to know about the cat vaccine.

The feline leukemia vaccine does not work very well. This retrovirus vaccine is a hazard because you have to test the cat for the retrovirus before you give the vaccine. If you give the vaccine to a cat that has the retrovirus, it breaks down the immune system. The cat generally gets sick, and most of them die. In 1986 or 1987 the California Veterinary College, in collaboration with the Primate Center people, discovered the FIV [Feline Immunodeficiency Virus]. It came from a cat in San Francisco and is more closely related to SIV and HIV than to feline leukemia. Huebner had worked with a mouse retrovirus. There was a real interest in looking at other viruses by people who were "bench" scientists. They were not the Max Essexes and the Bob Gallos and the Murray Gardners getting together. These were people who were injecting the animals, growing viruses, and so on. That was another characteristic of this meeting that made it different. It was calculated to be that way, and it was. Dr. Salzman's book is an excellent review of the meeting.

Harden: Many scientists have used mice in their studies. Were the scientists concerned with the cost of primate models, or did they use mice for certain specific things and then come back to primates for other studies? How do you determine which model is going to be the best?

Gay: People who are determined to study AIDS but who cannot afford the primates will probably turn to the mouse retrovirus. I do not know the mouse retrovirus system very well, but it is not nearly as similar to human AIDS as is SIV in the primates, in terms of the infected white cells having some similarities. Probably the mouse is not a bad place to screen, but you can do a fair amount of screening in tissue cultures of the white cells infected with the virus. I do not think the mouse is a major model for AIDS, except in the SCID [Severe Combined Immunodeficiency Disease] mouse. Are you familiar with that?

Harden: No.

Gay: Do you remember the Houston bubble baby? The SCID mouse is a bubble baby mouse. It essentially has no immune system. You can sew human skin on the mouse's skin and it will survive; the skin will grow. Furthermore, if you inject human white cells into a SCID mouse, the white cells will set up housekeeping and reproduce. Now you have a mouse that has a human immune system which you can infect with AIDS.

Harden: You noted that budget expansions for AIDS were incredibly rapid. The amounts doubled between 1983 and 1984. They doubled again in 1985. AIDS research began to overshadow other research projects in the primate centers. Could you elaborate on that a little?

Gay: I do not think so. That pretty well covers it.

Harden: Did the centers drop research in progress? Were they able to hire more people to keep some projects going? What does "overshadow" mean in this context?

Gay: It means that AIDS research received all the new space and all the new money, as well as all the attention and publicity. I do not know of any major projects that were discontinued, however. Much ophthalmology research was going on at the New England center and at Atlanta. None of that was dropped. A lot of work on other infectious diseases was being done at Delta, Tulane, and California. None of that was dropped. Reproductive biology was a major focus at the Oregon center. I do not think any of that was dropped. There may have been a few infectious diseases projects that fell by the way as people turned their attention to AIDS, but I do not think that any other major projects were dropped.

One of the two things that are very important at the primate centers is neuroscience research. Working with an animal with an extremely well-developed nervous system and reproduction system is important simply because they are very similar to humans. I do not think that any projects in the neurosciences or in reproduction were dropped. Probably none of the behavioral science projects were dropped, either, because behaviorists do not have much of a role in infectious disease work. In fact, there are some behaviorists who do not believe in the infectious disease theory. At least, that is the belief of some of us who have to work with them. You cannot seem to convince them that you cannot put all the animals together and keep them well. Overall, I do not believe that many projects were dropped because of AIDS.

Harden: Did the new money and the status associated with AIDS cause any problems between people?

Gay: Yes. But I do not remember any crises because of it. Dr. Leo Whitehair could probably answer that in greater detail.

Harden: In the summary of the 1986 Napa Valley meeting, Dr. Gardner was very enthusiastic about certain models for AIDS. However, in Dr. [Jorge] Ribas's document, dated 27 October 1986--it was the background for the December 1986 conference sponsored by Walter Reed Army Medical Center--he said in bold type that there were no satisfactory <u>in vivo</u> models for AIDS. What was he talking about? Why would he say that?

Gay: I do not know.

Harden: Did a whole group of people think that there were no good models?

Gay: There is a group of people who are very disappointed because there is not an animal into which you can put HIV and get AIDS. Ribas is part of that group.

Harden: What was the connection of the groups working with the Army on AIDS? What was the Army's interest other than protecting its own personnel?

Gay: To avoid getting credit for spreading AIDS overseas.

Harden: So you are saying that they were looking for an animal model that could be infected with HIV rather than exploiting the SIV model?

Gay: The Army always wants a quick answer.

Harden: Did the primate centers work well with the Army? I believe they accepted a number of contracts from the Army.

Gay: As the person who administered the program, I feel that, yes, we did work well together. We received a large contract from the Army that Dr. Dennis Johnsen managed. The centers and the Army worked very well together. I found Ribas a good man to work with. Do you know Colonel [Donald] Burke? Colonel Burke is the [Dr.] Anthony Fauci of the Army. He is in a class with Tony, too. He is very good. Burke and [Dr. Robert] Redfield--who is a very good scientist but who is also a little cynical; he occasionally makes colleagues angry--are always looking for an answer. Burke is spearheading a vaccine trial in Thailand now. He is very well informed. He and two other researchers have certain advantages because they can examine their population in the army closely. When troops come in, they can examine the population annually, and they can check whenever anyone goes through the hospital. As a result Burke has the best epidemiological records on AIDS in the world, except those of the former Soviet Union. I once asked him about the incidence of AIDS in Africa. When he told me, I asked where his data came from, since he did not do the tests himself. He replied, "I exchange information with the Soviets, and they test everybody who comes in." He really was busy globally. Burke is a great contributor in this field; anybody who was thinking of having a meeting on AIDS should include him. I have always found the military nice to work with. That is not the case with many of my colleagues. But I had a good time in the Defense Department and I have had a good time with the Defense Department researchers since I left.

Harden: Is it better doing research on animals since you can exert control over variables like diet that you may not be able to regulate in humans? Do you get your results faster that way?

Gay: I think the results of studies with animals are more reliable. The rate at which results are obtained depends on the animal being studied because animals generally have a shorter life span than humans, except possibly the chimpanzee. Due to this shorter life span of the animal, some pathogenic agents have a shorter incubation period. This means you can get enough data for a paper in less than five years which is fairly quick.

Harden: When I interviewed Ken [Dr. Kenneth] Sell at Emory in 1988, he commented that everybody was concerned over the new finding that SIV isolated from a sooty mangabey suddenly seemed to have mutated to a highly virulent form.

Gay: I remember that very well.

Harden: Could you elaborate on what happened and what the outcome of that incident was?

Gay: The outcome was that the agent became a standard for testing in the macaques. You got quicker results that way. That episode bothers me because retroviruses modify all the time, and HIV could mutate into a highly pathogenic form. HIV-2 from West Africa is not so pathogenic. Viruses that are not so pathogenic are going to die off. I do not know what is going to happen when we get a more pathogenic one. We have seen it happen in the cat--that FIV cat from California. We have seen it in the primate virus--the one from Emory. Stay tuned for it to happen with HIV.

Harden: If I remember correctly, if a virus mutates to a form that kills its host rapidly, the only way it can continue to survive and reproduce is by finding a quicker route of transmission. If HIV mutated to a virulent form that was transmissible through the air by sneezing, we would be in bad shape.

Gay: Yes. I do not know of any retrovirus that has airborne transmission. But, yes, we would be in bad shape. That happened with the Pasteurella organism. I am reading a book on the effect of infectious diseases on history. The author talks about plague, which began with the bubonic form. When a pneumonic form appeared that was transmitted by sneezing, it moved a lot faster.

Harden: Could you bring us up to date on what has been happening in animal research on AIDS during the last three years, since about 1989, and what you see as the important lines of research now?

Gay: I really have not been going to the meetings and keeping up, so I do not think you should take my comments as authoritative. I have been following very closely developments with the pigtail macaque, which have been very interesting. In terms of host susceptibility, one has to ask whether the people in Seattle are working with the same virus that we were working with in 1985, because that virus changes all the time. Maybe Dr. Ribas will finally have his model. Another very interesting development is the SCID mouse model that I mentioned. I think that is going to provide an excellent means for screening potential AIDS drugs, but I do not know whether that is going to be better than Tom [Dr. Thomas] Kindt's rabbits--he's still struggling with those--or than [Dr. Malcolm] Martin's mice. You can do marvelous things with transgenic animals, and the researchers may get one yet that is more susceptible. We also have plenty of chimpanzees now, though I notice that writers like Gina Kolata, who writes for The New York Times, say that there are not enough chimpanzees. There are plenty of chimpanzees for vaccine trials now.

Harden: Do you think that any of the candidate vaccines being developed look promising, or is the mutation of the virus so fast that none of them will be able to provide protection?

Gay: I think that producing immunity against these retroviruses will require an entire system of immunization. It will not be like immunization against flu or polio--three shots and you are immune. It will take a bigger boost than that. [Dr. Harry] Myers, who used to be in the Bureau of Biologics and now is at Los Alamos, has been tracing the enormous differences in the HIV viruses that he has isolated from around the world. Nobody says this, but as a less than well trained immunologist, my interpretation is that the whole thing may be a kind of a lottery: if you take the vaccine, you will be immune to some strains but not to others. That is why I think it will take some system of immunizing beyond just one or two shots. It will be a real struggle to get a vaccine that will protect against all kinds of AIDS.

Harden: Would you make an overall assessment of the contribution of primate models and other animal models to research on AIDS?

Gay: My assessment is that most of the really good basic research has depended on animal models. This has been a more animal model-dependent disease than most that we have experienced, because we do not have any human patients who have survived. We are even more controlled on what can be done with patients than we used to be, but we have dozens of agents all the time that we need to screen. DdI [2'-3'-dideoxyinosine], AZT [3'Azido2',3'-dideoxythymidine], the antibiotics, all of those things have been screened against animal retroviruses before they have gone to the clinics. Another point to note is that there has been an evolution in animal models since AIDS was identified in 1980. With transgenic technology, which we are not able to apply to rats yet but which is being applied to some other animals--sheep, cattle, and mice--we can create types of susceptibility that were not possible before. We have the SCID mouse, in which we can do screening that we could not do before. Thus there has been a real evolution of animal models, which may help.

Harden: Do you think the public understands the importance of animal models?

Gay: No.

Harden: What should be done to change that?

Gay: Something should be done to change the public's view on the use of animals in all types of biomedical research. Look at the work Tom [Dr. Thomas] Starzl has done on organ transplantation. Starzl was a grantee of NIAID in the late 1960s. All of the work done by immunologists has also accrued to help the AIDS campaign. But all of this research has been extremely important for successful organ transplantation, even the techniques needed by surgeons in order to do it. I was glad to see [Dr. Joseph] Murray at Harvard finally get the Nobel prize for his kidney transplant work. [I was very interested that he gave a lot of credit to a chap from England, named Dr. Roy Yorke Calne. He is now chairman of surgery at Cambridge. Murray wrote a chapter for me in volume II of my book, "Methods of Animal Experimentation." He gave a lot of credit to Calne for bringing the basic immunology from [Dr. Peter] Medawar's lab to Murray's lab.] Medawar was a great immunology animal experimenter. I think it is interesting. But the public really is not much interested in this sort of thing.

Harden: Just the final results.

Gay: No, they are not interested in research in animals, but the importance of research animals is clear and it does make a big difference. I think it is unfortunate that we find animal rights material being presented to school children now, because that is going to create a problem. If you had occasion to practice veterinary medicine you would understand. I had a real dose of this in New York City. "You say my dog has worms? Well, what's that?" "Do you know what an angleworm is?" They did not know what an angleworm was. They had never seen a worm. Increasingly as we recruit people to work in the laboratory animal field, we find that we have much more training to do, because now our student population comes to us biologically illiterate. That causes a problem in understanding the environment, and the crisis we now face. I have talked with people working in AIDS education. You have to teach people biology before they understand where AIDS is coming from and what it will do to them. I guess, biology is not interesting to many people, and I do not know how to make it glamorous. I am not a good educator, but it must be done if we want to help people.

Harden: Thank you very much, Dr. Gay.